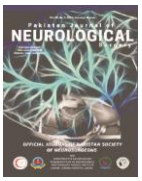

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Original Article (BRAIN)

Increment of High-Grade Gliomas Among Pediatric and Young Adult Population

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ABSTRACT

Background/Objective: Glioblastomas are among the commonest primary brain cancers. This study aimed to assess the trend shift of high-grade glioma in our setting among the young and pediatric population.

Materials and Methods: This is a descriptive and cross-sectional study; it was carried out at the Department of Neurosurgery, Liaquat University of Medical and Health Sciences, between duration. All cases with suspected brain tumors, irrespective of age or gender were assessed for glioblastoma. Once a solid tumor was identified on imaging with consistent features of glioblastoma, a provisional diagnosis was established. After that, the patient underwent a brain biopsy. Patients' gender, demographics, clinical presentation, radiologic records, etc. were collected in a predefined proforma.

Results: 22 patients were diagnosed with glioblastoma with a high frequency of patients between the age range of 20 to 30 years. The most common location of the tumor was subcortical near the midline. There was slight male predominance. 8 patients had levels of KPS at presentation < 70 and among those two were infants, four were in a vegetative state, and two had a loss of consciousness secondary to increased intracranial pressure. The recurrence rate among those who came back for follow-ups was 27.2%.

Conclusion: Though it is a short study with short follow-up results were astonishing due to perhaps trend shift among Glioblastoma patients, a further detailed workup is needed in different dimensions especially molecular level and genetics to know exactly about the disease and the national registry should be carried and alarmed to identify the problem at once, counter effectively and make a future strategy.

Keywords: Trends, Inclination, Glioblastoma, Young, Brain Tumor.

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INTRODUCTION

Primary brain tumors among the adult population are among the most lethal of all adult cancers.[1,2] The incidence of such cases is raised in recent times and has been reported,[3] but it is questioned that was is the actual reason behind this raising trend is whether these cases are increased due to evolution in radiologic techniques in recent times or any risk factor that is not identified yet or even true rise of such cases.[4]

Such primary brain tumors vary in histologic type of the tumor some may vary tissue from which they originated.[5] There may be so many reasons being evaluated, among such factors are Genomic, Immunohistologic, biochemical factors, and environmental determinants, encompassing physical. According to literature, this burden of disease is much higher in old age although less often it is also reported in the younger and middle-aged population. However, in some studies, the age group is 30 – 60 years.[6]

Current epidemiological literature reveals the frequency of glioblastoma in Western countries is 2 – 3 per 100,000 adults annually,[7] and the number of new cases every year in men in comparison to women are at the level of 1.26: 1 [8]. Cases of glioblastoma in the pediatric population have also been reported. It is approximated that the incidence of glioblastoma is 1.1 to 3.6 per 100 000 infants,[9] with the frequency of 3.3 male infants to one female child with glioblastoma.

Since glioblastoma is aggressive cancer, the overall patient prognosis with respect to morbidity and mortality is quite high, even after early and proper treatment. Over 85% of patients die within two years. Since we are seeing a considerable variance in the epidemiology of this disease and has a high mortality, we undertook the current study intending to evaluate the inclination of glioblastomas among young patients.

MATERIALS AND METHODS

Study Design & Setting

A descriptive, cross-sectional study was conducted at the Department of Neurosurgery, Liaquat University of Medical and Health Sciences, between the duration of June 2020 to Jun 2021. After procuring ethical approval from the institutional review board committee, the study was initiated. A Nonprobability sampling was considered. All patients who meet inclusion criteria and were admitted in a single year were taken as samples.

Clinical Management and Data Collection

All cases with suspected brain tumors, irrespective of age or gender were assessed for glioblastoma. Informed consent was requested from all the patients. The patients who presented with chronic headaches, seizures, and hemiparesis were vigilantly examined and underwent magnetic resonance imaging. Once a solid tumor was identified on imaging with consistent features of glioblastoma, a provisional diagnosis was established. After that, the patient underwent a brain biopsy. Under aseptic conditions, an experienced surgeon performed the biopsy with a needle before the excisional surgery or during the surgery depending upon the surgeon's discretion and the patient's clinical profile.

Karnofsky Performance Scale (KPS) score was also evaluated for each patient which highlighted the prognosis and determined the most optimum approach in the management of glioblastoma. Patients with low preoperative KPS values (< 70) have shorter overall survival rates.[10]

All information regarding the patients' gender, age, demographics, clinical presentation and symptomatology, radiologic findings, KPS at presentation and repeat KPS before surgery, treatment modality, and histopathological reports were collected, and whether patients underwent

chemo/radiotherapy or not, and prognosis with follow-up statistics was recorded in a predefined pro forma. All data were entered into an excel sheet and the data was presented in tabular form.

Inclusion Criteria

All patients in-between ages 0 to 40 years were included, Either sex was included in the study, and all Patients whose MRI Brain scans with findings relating to High-grade gliomas and with biopsy proving high-grade gliomas were included in the study.

Exclusion Criteria

Patients or attendants who were not willing to be part of the study, patients who did not undergo surgery, and patients who do not have any biopsy records along with patients having KPS< 70 were excluded from the study.

Statistical Analysis

Because the data was very small and simple proforma-based information was recorded and then analysis was carried out through SPSS version 26.0. All data was put and results were accomplished.

RESULTS

Clinical Information

During the study, a total of 22 patients with a median age of 26 years and a range of 10 – 39 years were diagnosed with high-grade glioblastoma. Out of the total 22 patients who were diagnosed with Glioblastoma, about 13 (59.1%) occurred in male patients. Furthermore, one-half of the patients were between the ages of 20 and 30 years. The majority were asymptomatic while in at least 40 percent of the patients, increased intracranial pressure was observed (Table 1).

Table 1: Clinical Characteristics of Study Patients.

Characteristics	N (%)
Median Age (years)	26
Gender	
Male	15 (68.2%)
Female	7 (31.8%)
Age Groups	
<10yr	1 (4.5%)
11-20yrs	6 (27.2%)
20-30yrs	11 (50%)
30-39yrs	4 (18.1%)
Sign and Symptoms	
Asymptomatic	16 (72.7%)
Seizures	5 (22.7%)
Refusal to feed	2 (9.1%)
Any other focal deficit	8 (36.3%)
Increased intracranial pressure	9 (40.9%)
Loss of Consciousness	2 (9.1%)
Vegetative	4 (18.1%)

Location of Glioblastoma

In six patients (27.2%), the lesion was at the subcortical region near midline while, in five patients the lesion was located in the parietal lobe, and in another five patients the lesion occupied a combined frontal, parietal, and

Table 2: Location of Glioblastoma in Study Population.

Region	Total (n = 22)	Male (n = 13)	Female (n = 9)
Parietal	5 (22.7%)	2 (15.4%)	3 (33.3%)
Temporal (only)	0	0	0
Frontal	3 (13.6%)	2 (15.4%)	1 (11.1)
Occipital (only)	0	0	0
Subcortical near midline	6 (27.2%)	6 (46.1%)	0
Brain stem	3 (13.6%)	0	3 (33.3%)
Mix Frontal /Temporal / Parietal	5 (22.7%)	3 (23.1%)	2 (22.2%)

temporal lobes. Upon further stratification, it was revealed all tumors in the subcortical region were found in male patients (Table 2).

KPS, GCS, and Radiochemotherapy

KPS level at presentation revealed that eight patients had levels < 70 and among those two were infants, four were in a vegetative state, and two had a loss of consciousness secondary to increased intracranial pressure. 14 (63.6%) had KPS of > 70.

19 patients underwent surgical resection of the tumor and one patient was offered fine needle aspirate cytology (FNAC). KPS levels were measured postoperatively which revealed that out of the 19 patients, 18 (81.8%) had KPS levels greater than 70. 10 (45.45%) patients underwent both radio- and chemotherapy (Table 3). Two infants were unable to get chemo- or radiotherapy and three patients were unfit for chemo- or radiotherapy because their condition deteriorated (brain swelling and decreased GCS).

Table 3: Clinical Findings and Management of Patients.

KPS level at presentation (n=22)	
< 70	8 (36.4%)
> 70	14 (63.6%)
KPS level postoperatively (n=19)	
< 70	1 (5.2%)
> 70	18 (81.8%)
GCS at 1st Surgery	
< 8	5 (22.7%)
8 – 13	5 (22.7%)
> 13	12 (54.5%)
Radiochemotherapy	
Unfit for radiotherapy and chemotherapy	5 (22.7%)
Both radiotherapy and chemotherapy	10 (45.45%)
Absent/Lost to follow-up	7 (31.8%)
The average number of surgeries	
1 surgery	16 (72.7%)
2 surgery	2 (28.6%)
3 or >3 surgeries	1 (5.2%)
Conservative	2 (28.6%)
Fine needle aspirate cytology	1 (5.2%)

Recurrence

The recurrence rate among those who came back for follow-ups was 27.2%. Out of the 22 patients, five patients came back positive after primary surgery, three of which were operated on multiple times while 2 did not admit again for surgery and went to some other center for further management. While 16 patients came for initial follow-up for the first 6 – 8 months in the outpatient department but were lost afterward.

Mortality

Since only a few patients maintained follow-up visits after 8 months postoperatively, therefore, the mortality rate as such could not be assessed. Out of those who maintained follow-up, one male in a vegetative state expired 4 months after 1st surgery. He had a thalamic glioblastoma near the midline. Two female patients expired after multiple surgeries. Out of these women, one expired after 8 months and the other died six months postoperatively. Both had parietal tumors that extended towards the subcortical region.

Lifespan

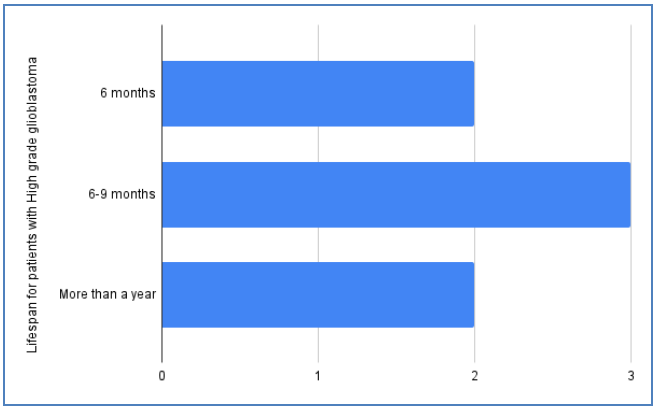

Figure 1: Lifespan for patients with High-grade glioblastoma.

2 patients expired within 6months, while 3 patients survived the initial 9 months. One expired after 8 months but the latter were lost to

follow-up. Two patients survived for nearly 10 years of the first surgery (Figure 1).

Radiological Findings

Radiological features (Figures 2-4) include perilesional edema and irregular enhancement pattern with a central necrotic core. In 6 patients the tumor was large, extending towards the midline. 5 had tumors restricted to the parietal region, while in 5 patients more than one lobe was involved, and 3 patients had frontal lobe and brain stem involvement, respectively. Interestingly all three patients with brain stem involvement were females.

DISCUSSION

Glioblastomas are known to be one of the most aggressive cancers that are found in the spinal cord and brain. They are made up of astrocytes which in turn support nerve cells. Glioblastomas are mostly seen in older adults.[11] However, the present study highlighted the alarming situation in our center where twenty-two cases of glioblastoma were studied with a mean age of 26 years. Existing evidence shows that the peak incidence rate of glioblastoma is between 70-79 years however, in our study a much younger population was observed.[12] A unique case was reported by Caroli and colleagues on intramedullary glioblastoma in a six-year-old child who had a very rapid clinical presentation.[13] A case series study however reported that glioblastomas usually happen in the 3rd decade of life, the mean age being 28.5 years.[14] Furthermore, a slight male predominance was also seen in an 18-year study by Chen et al. which is consistent with the current study.[15] The results of the present study were astonishing due to a trend shift seen among glioblastoma patients (Figure 1).

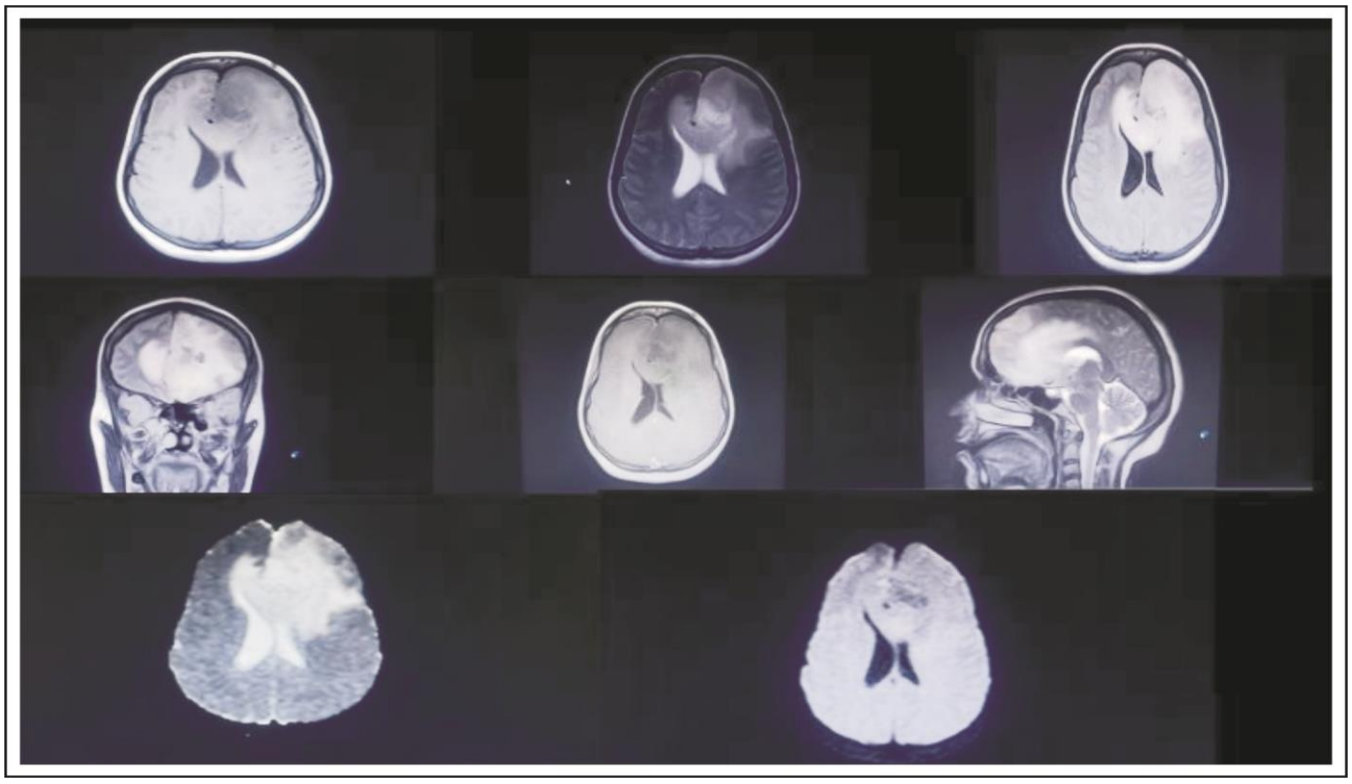

Figure 2: A 30-year-old female with frontal high-grade glioma. (Images used with permission)

Young et al. in their review of the current guidelines for the management of elderly patients discussed the elderly population to be managed quite conservatively than the younger population since the elderly have high operative risks and are more likely to suffer from side effects of radiotherapy and chemotherapy.[16] In our study out of the seven patients who underwent radiotherapy following surgery, 4 (57.1%) died. In contrast, certain studies report a more favorable outcome for younger patients diagnosed with GBM. Certain molecular mutations among younger patients with primary GBM may contribute to a more favorable outcome. For instance, Herrera-Oropeza in their study compared the younger population with the elderly population and found that the young population is regulated by different transcription factors (TFs) and so it behaves differently from the elder population thereby, giving them a better prognosis of the disease, the elderly however had a survival rate of < one year.[17] Similarly, Leibetseder et al. also found young age to be a good prognostic factor for patients diagnosed with GBM (glioblastoma multiforme) since a high frequency of MGMT promoter methylation (61.1%) and IDH1 mutations (39.3%) were seen in the young age population leading to a good outcome.[18] Nevertheless, in our study, these mutations were not assessed due to resource constraints.

In the present study, the most common lobe involved was the parietal and frontal lobe with presenting symptoms including headache, seizures, and hemiparesis (Figure 2).

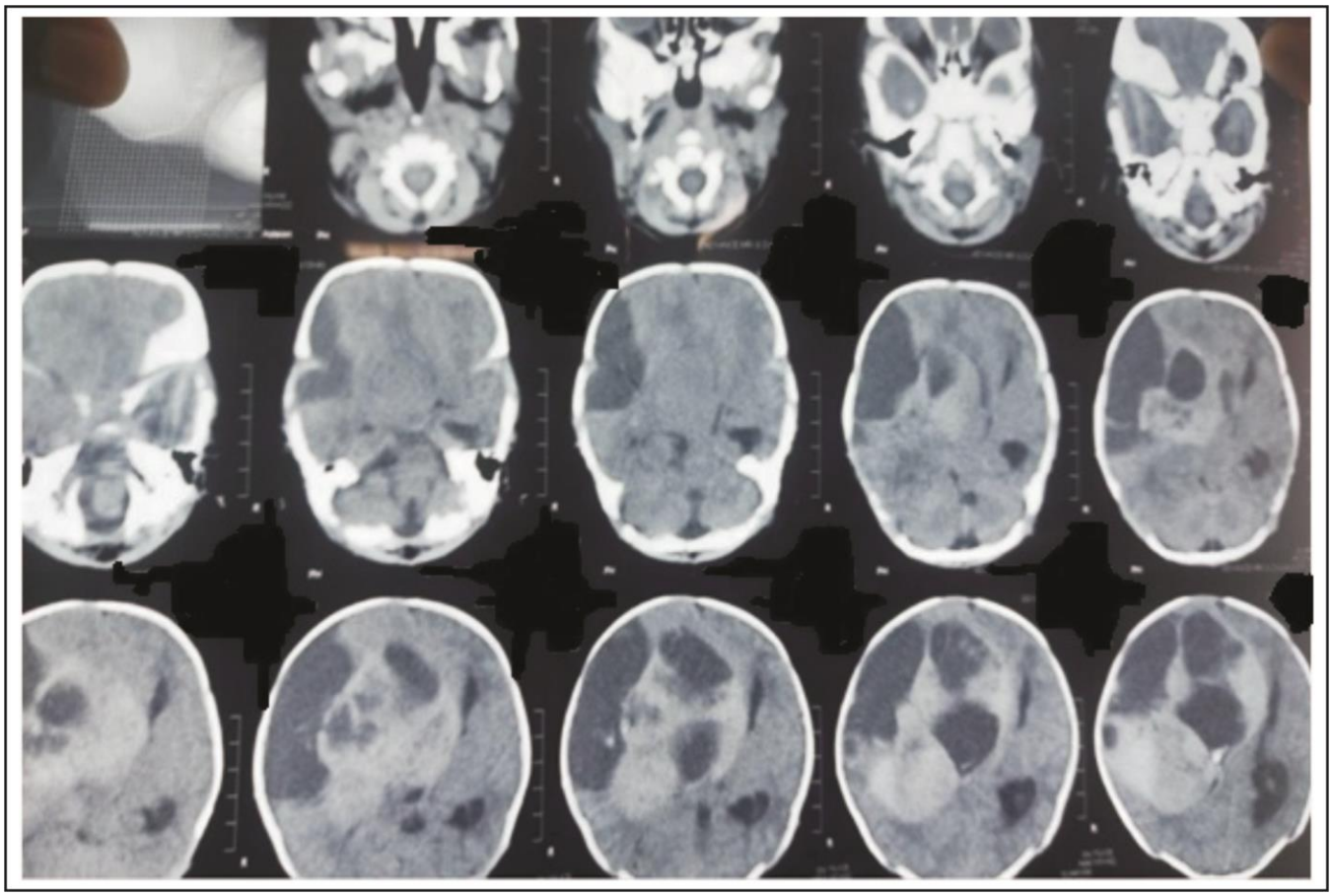

Figure 3: Pediatric Malignant High-Grade Glioma - Grade IV. (Images used with permission)

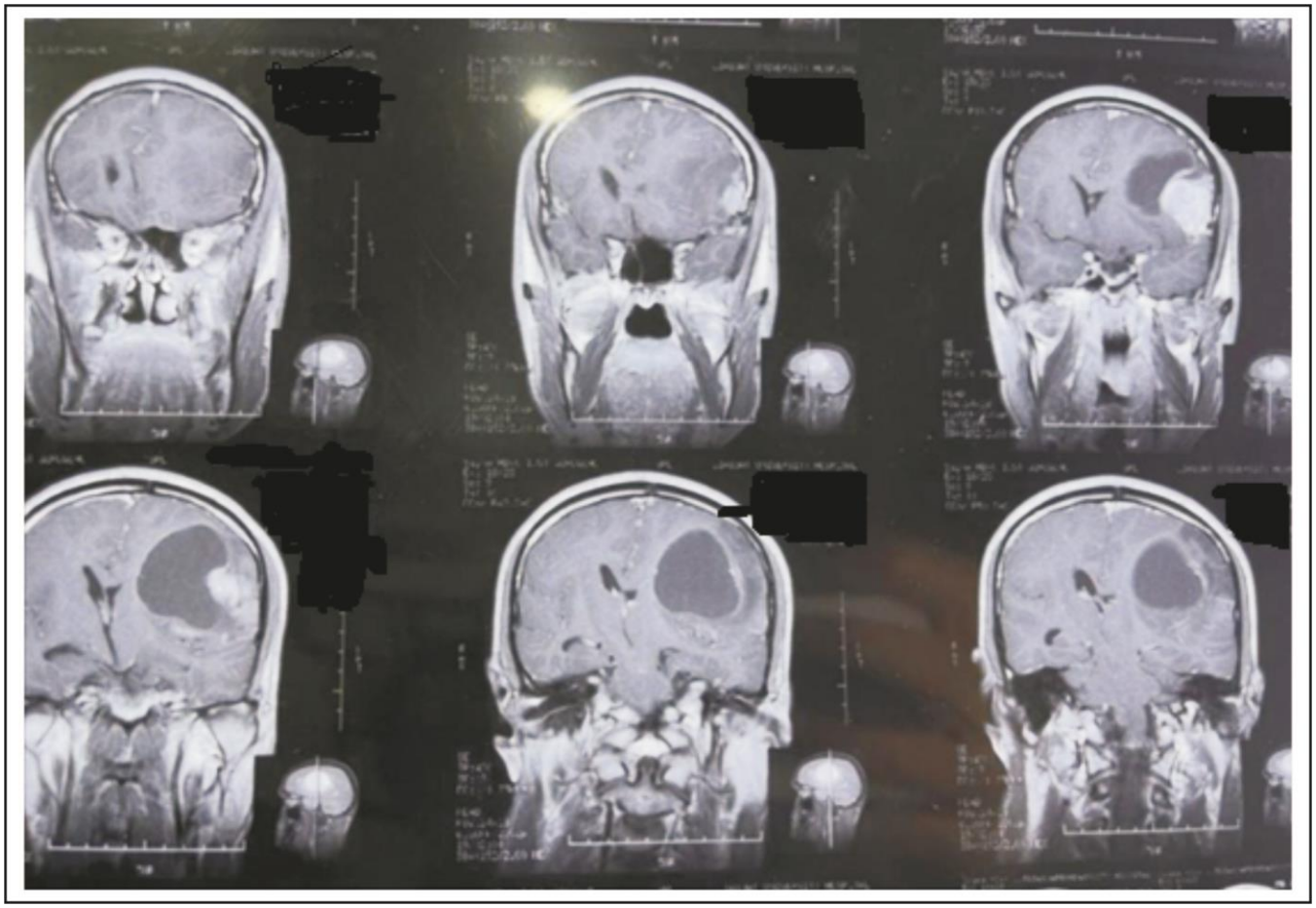

Figure 4: 25-year-old male with left-sided high-grade glioma. (Images used with permission)

In a study by Nizamutdinov et al. the tumor sites that were linked to good survival outcome included the occipital (8.1% vs. 2.9%; p = 0.05), parietal (24.2% vs. 20.8%; p = 0.05) and temporal lobe (25.8% vs. 20.2%; p = 0.03) and sites with poor prognosis included brain overlapping (4.6% vs. 10.2%; P = 0.15) and GBM not otherwise specified (4.8% vs. 10.1%; P = 0.18).[19]

In Yuile's study, the age of < 60 had a significantly higher one-year survival (p < 0.0007). Furthermore, the study also showed a correlation between tumor location and survival; patients with GBM in frontal, parietal, and post fossa had a one-year survival rate of 44.3% versus 14.1% for patients with GBM in the temporal, midline, or occipital lobe (p = 0.0002).[21]

Eighteen patients in the study presented with a preoperative value of KPS of more than 70 however, four patients had a KPS of below 70. After confirmation of diagnosis with biopsy, seven patients underwent radiotherapy after surgery, and out of these, four expired by six-month follow-up while two were lost to follow-up. The KPS (Karnofsky Performance Scale) score is utilized to classify the prognosis of patients and to find the required treatment protocol for GBM (Glioblastoma multiforme).[22]

Chambless reported a median preoperative and postoperative KPS scores were 70 and 80, respectively. Postoperatively, 92 (57%) individuals experienced an increase in their KPS score, 40 (25%) remained unchanged, and 29 (18%) cases were reduced. Higher postoperative KPS and younger age of patients were significantly

associated with better overall survival; p = 0.0001 and p = 0.0443, respectively.[21]

Our study was limited due to a small number of patients and a rather restricted follow-up period. This limits the generalizability of the study findings to a larger population. Though it is a short study with a short follow-up, results were astonishing due to perhaps a trend shift among Glioblastoma patients. Further detailed workup is needed in different dimensions especially molecular level and genetics to know exactly about the disease. A national registry should be carried out and alarmed to identify problems at once, counter them effectively and make future strategies.

CONCLUSION

The present study highlighted a shift in the trend of Glioblastomas which is intriguing and warrants further research. This study is an alarm to identify problems at once, and a nationwide study should be conducted to counter effectively and make a future strategy to deal with such issues.

RECOMMENDATION

A national tumor registry should be done also further research work on gliomas is warranted in similar dimensions and other dimensions to not only know the exact number of such patients but also genetic, molecular, and immunohistochemical research should be carried out to identify pathology more properly and to coup this pathology.

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Additional Information

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Human Subject: Consent was obtained by all patients/participants in this study.
Conflict of Interest:
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AUTHORS CONTRIBUTIONS

Ser. #	Authors Full Name	Intellectual Contribution to Paper in Term of:
1.	Peer Asad Aziz	Study design and methodology.
2.	Muhammad Hamid Ali	Paper writing, referencing, data calculations.
3.	Sanaullah Pathan	Analysis of data and interpretation of results.
4.	Mubarak Hussain	Data collection and calculations.
5.	Suhail Ahmed Aghani	Literature review and manuscript writing.
6.	Riaz Ahmed Raja	Analysis of data and quality insurer.